GUIDANCE[1]

CAPTOPRIL TABLETS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. INTRODUCTION

A. Clinical Usage/Pharmacology

Captopril, an antihypertensive, inhibits the enzyme which converts angiotensin I, a relatively inactive decapeptide, to angiotensin II, a potent endogenous vasoconstrictor substance. This enzyme, angiotensin converting enzyme, or ACE, is a peptidyldipeptide carboxy hydrolase (1).

The recommended initial dosage for treatment of hypertension is 25 mg bid or tid. This can be increased to 50 mg bid or tid after one or two weeks if the lower dose is ineffective. Doses of captopril higher than 50 mg bid are recommended only with concomitant administration of a thiazide diuretic (2).

Captopril is marketed by E.R. Squibb & Sons, Inc., under the trade name Capoten [R] in scored oral tablets of 12.5, 25, 50, and 100 mg. Inactive ingredients are microcrystalline cellulose, corn starch, lactose, and stearic acid (2).

B. Chemistry

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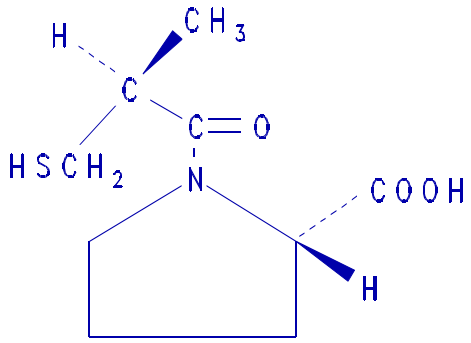
[1] This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-295-8290; Fax: 301-295-8183).

The chemical name of captopril is (S)-1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline. Its chemical formula is $C_9H_{15}NO_3S$, and its molecular weight 217.28. Captopril is a white to off-white crystalline powder which is soluble in water (approximately 160 mg/ml), methanol, and ethanol and sparingly soluble in chloroform and ethyl acetate (3). The chemical structure of captopril is given below:



Captopril

C. Pharmacokinetics

Following oral administration, approximately 60-75% of the dose of captopril is rapidly absorbed from the gastrointestinal tract in fasting healthy adults or hypertensive patients. Peak blood levels of unchanged captopril occur about one hour after oral administration (2,4). Areas under the concentration-time curve and maximum blood concentrations after single oral doses of captopril appear to be dose-related over a range of 10 to 100 mg (5). Approximately 25-30 percent of the drug in the systemic circulation is bound to plasma proteins. Because the presence of food in the GI tract is reported to reduce absorption of the drug by 30 to 40 percent, captopril is labeled to be dosed one hour before meals. Blood pressure reduction is usually maximal 60 to 90 minutes post-dose. The elimination half-life of captopril is reported to be about two hours.

About half the absorbed dose of captopril is rapidly metabolized, mainly to captopril-cysteine disulfide and

to the disulfide dimer of captopril. Captopril and its metabolites are excreted in the urine. Renal excretion of unchanged captopril occurs via tubular secretion. In patients with normal renal function, more than 95 percent of the absorbed dose is excreted in the urine in 24 hours. About 40-50 percent of the drug excreted in the urine is unchanged captopril.

II. *IN VIVO* BIOEQUIVALENCE STUDY[2]

A. Product Information

1. FDA Designated Reference Product: Capoten® Tablets, 100 mg (Squibb)

2. Batch size: The test batch or lot must be manufactured under production conditions and must be of a size at least 10% that of the largest lot planned for full production or a minimum of 100,000 units, whichever is larger.

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5%.

B. Type of Study Required

1. A single-dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting conditions comparing 100 mg doses of the test and reference products is required.

C. Recommended Protocol for Conducting a Single Dose Bioequivalence Study Under Fasting Conditions

Objective: To compare the rate and extent of absorption of a generic formulation with that of a reference formulation when given as equal labeled doses.

Design: The study design is a single dose, two-treatment, two-period, two-sequence crossover with a

[2] The sponsoring firm is advised that an Investigational New Drug Application (IND) filing may be required if dosing levels exceed those recommended in the official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1).

one-week washout period between Phase I and Phase II dosing. An equal number of subjects should be randomly assigned to each of the two possible dosing sequences. Before the study begins, the proposed protocols should be approved by an institutional review board.

Facilities: The clinical and analytical laboratories used for the study should be identified along with the names, titles and curriculum vitae of the medical and scientific/analytical directors.

Selection of Subjects: The sponsor should enroll a number of subjects sufficient to ensure adequate statistical results. It is recommended that a minimum of 24 subjects be used in this study. Subjects should be healthy male volunteers aged 18 to 50 years and within 10% of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical examination, and clinical laboratory test results. Subjects with any current or past medical condition which might significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. Written, informed consent must be obtained from all study participants before they are accepted into the studies.

Procedures: Following an overnight fast of at least 10 hours, subjects should be given a single 100 mg dose of the test or reference product with 240 ml of water. Subject blood pressure and pulse rate should be measured immediately before drug administration (pre-dose) and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose.

Restrictions: Study volunteers should observe the following restrictions:

a. Water may be allowed except for one hour before and after drug administration when no liquid should be permitted other than that needed for drug dosing.

b. Subjects should fast for at least four hours after administration of the test or reference treatment. All meals should be standardized during the study.

c. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

d. Subjects should take no Rx medications beginning two weeks and no OTC medications beginning one week before drug administration and until after the study is completed.

Blood Sampling: Venous blood samples should be collected pre-dose (0 hours) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, and 10 hours post-dose. Whole blood or blood plasma may be used for the assay. In either case, the blood samples should be chemically stabilized immediately after collection (see below). If plasma is to be assayed, it should be separated promptly from the stabilized whole blood. The whole blood or blood plasma samples should then be immediately frozen until assayed. Following a minimum one-week washout period, subjects should begin the second phase of the study.

Analytical Methods: Captopril should be measured in an appropriate biological matrix such as whole blood or blood plasma. Several assay methods are available (6,7,8). The method chosen should be validated to demonstrate adequate sensitivity, specificity, linearity, recovery, and accuracy and precision (both within and between days). Because the thiol group of captopril is readily oxidized, a chemical stabilizer must be added to the blood samples immediately after collection. Stability of the samples under frozen storage conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. Chromatograms of the analysis of the unknown samples, including all associated standard curve and Q.C. chromatograms, should be submitted for one-fifth of the subjects, chosen at random. The sponsor should justify the rejection of any analytical data and provide a rationale for selection of the reported values.

Statistical Analysis of Pharmacokinetic Data: See Division of Bioequivalence Guidance, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design."

Clinical Report and Adverse Reactions: Subject medical histories, physical examination reports and all incidents of possible adverse reactions to the study formulations should be reported.

Retention of Samples: The laboratory conducting the bioequivalence testing should retain an appropriately identified reserve sample of the test product and the reference standard used to perform an *in vivo* bioequivalence study for approval of the application. Each reserve sample should consist of at least 200 dosage units. For more information on retention of bioequivalence samples, please refer to CFR 21, 320.32.

III. *IN VITRO* TESTING REQUIREMENTS

A. Dissolution Testing

Conduct dissolution testing on 12 dosage units of the test product versus 12 units of the reference product. The biostudy lots should be used for those product strengths tested *in vivo*. The following dissolution method and tolerance is official in USP XXII and is recommended for this product:

Apparatus:	USP XXII Apparatus 1 (Basket) RPM: 50
Medium:	0.1 N HCL
Volume:	900 ml
Sampling Times:	10, 20, 30 minutes
Tolerance (Q):	NLT 80% (Q) in 20 minutes
Analytical:	U.V. abs. @ ca. 212 nm (USP XXII)

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in USP XXII.

IV. WAIVER REQUIREMENTS

A. Waiver of *in vivo* bioequivalence study requirements for the 12.5, 25, and 50 mg strengths of the generic product may be granted per 21 CFR 320.22(d)(2),provided both of the following conditions are met:

1. The lower strengths are proportionally similar in both active and inactive ingredients to the 100 mg strength, which has been demonstrated to be bioequivalent to the reference product *in vivo.*

2. The 12.5, 25, 50, and 100 mg strengths of the generic product meet the dissolution testing requirements.

V. REFERENCES

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